REMARKS

Summary of Office Action

In the Office Action, the Examiner rejected claims 1, 3, 4, 29, 31, and 32 under 35 U.S.C. § 103(a) as being unpatentable over an article by Lee et al. published in 2003 in the Journal of Microencapsulation (hereinafter referred to as "Lee"). The Examiner also rejected claims 1, 3-5, 26, 27, 29, and 31-35 under 35 U.S.C. § 103(a) as being unpatentable over Lee in view of U.S. Patent No. 5,690,954 (hereinafter referred to as "Illum"). Additionally, the Examiner rejected claims 1, 3-5, 27, 29, 31-33, and 35 under 35 U.S.C. § 103(a) as being unpatentable over Lee in view of U.S. Patent No. 5,529,777 (hereinafter referred to as "Andrianov"). Finally, the Examiner rejected claims 1, 3-5, 26-29, and 31-36 under 35 U.S.C. § 103(a) as being unpatentable over Lee and Andrianov in view of U.S. Patent Application Publication No. 2003/0074700 (hereinafter referred to as "Huang"). No other issues were presented.

Summary of Amendments

Upon entry of the present Response to Office Action, claims 1, 3, 5, 29, and 33 will have been amended. Additionally, claims 26-28 and 34-36 will have been cancelled and claims 37, 39-48, and 50-55 will have been withdrawn pursuant to the previous election. As such, claims 1, 3-5, 29, and 31-33 remain currently pending. Applicant respectfully submits that no new matter has been added by the amendments as support can be found in the originally filed specification at least at page 6, line 17; page 9, lines 10-15; and in the Examples. By the present amendment, Applicant submits that the rejections have been overcome and respectfully requests reconsideration of the outstanding Office Action.

Applicant's Response

1. Rejection over Lee

The Examiner submits that Lee discloses alginate microspheres which were coated ***or*** blended with the polymers HPMC, EUDRAGIT® RS 30D, ***or*** chitosan. *Office Action, Page 5* (emphasis added). The Examiner admits that Lee does not disclose a microcapsule encapsulating

an active ingredient with an inner layer of alginate/HPMC and an outer layer of chitosan. *Id.* In an effort to overcome this deficiency, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of the invention to prepare a microcapsule meeting these requirements due to the teachings of Lee. *Id.*

Applicant's independent claim 1 as currently amended recites, inter alia, "Polysaccharide double-layer microcapsules constituted by an outer layer of chitosan and an inner layer of alginate wherein they are obtained from solutions of alginate ... comprising the further polymer hydroxypropylmethylcellulose ...; from solutions of chitosan ...; from solutions of divalent ions ... the divalent ion functions as a gelification agent of the alginate to form single-layer capsules of alginate encapsulating at least one biologically active substance, and ... the divalent ion has a stabilizing function of the double layer microcapsule's outer coating of chitosan; wherein said at least one biologically active substance is lysozyme."

Similarly, Applicant's independent claim 29 as currently amended recites, inter alia, "Polysaccharide double-layer microcapsules constituted by an outer layer of chitosan and an inner layer of alginate wherein they are obtained through formation of single-layer capsules encapsulating at least one biologically active substance starting from solutions of alginate ... comprising the further polymer hydroxypropylmethylcellulose ... in which said substance is dispersed, by gelification ...; formation of the second coating layer of chitosan ... wherein said at least one biologically active substance is lysozyme."

Lee is understood to disclose alginate microspheres coated ***or*** blended with HPMC, EUDRAGIT® ***or*** chitosan, where the two methods of preparation of microspheres and the polymers are singularly considered. *See, e.g., last paragraph on p.190* ("To prevent a rapid drug release, alginate microspheres were coated ***or*** blended with polymers.) (emphasis added). Hence, Lee is understood to teach the use of the coating and the blending as equivalent possible *alternative* methods for preparing a controlled release drug delivery system based on alginate microspheres as well as teaching the polymers are equivalent possible alternatives.

This understanding is further supported by the fact that the HPMC-blended alginate microspheres and the chitosan-coated alginate microspheres give very similar results in terms of release (see Figures 4 and 7) and both provide an extended release of the drug. Moreover, Lee concluded that HPMC-blended alginate microspheres are a more convenient drug delivery

system, both for the preparation and for the controlled drug release, compared with chitosan-coated microspheres. *See Conclusion on pp. 190-91.*

As such, although the Examiner admits that Lee does not explicitly teach a microcapsule encapsulating an active ingredient with an inner layer of alginate/HPMC and an outer layer of chitosan, it is respectfully submitted that neither does Lee suggest microcapsules where the inner layer is of alginate ***blended*** with HPMC and said inner layer is further ***coated*** with a layer of chitosan as in the case of Applicant's claimed invention. In fact, Lee's focus was on developing an improved controlled drug release system and further taught that HPMC-blended alginate microspheres are more easily made and used due to a convenient process and controlled drug release, in comparison to chitosan-coated microspheres. *See, p. 191.* Accordingly, a person having ordinary skill in the art upon reading Lee would refrain ***from combining the blending of HPMC with alginate and the coating of HPMC-blended alginate microspheres with chitosan***, since Lee discloses that the HPMC-blended alginate microspheres give a useable result, the combination of the two is not taught or suggested as giving a better result, and, on the contrary, could impair the drug release. Actually, by HPMC-mixing with alginate and the further coating of the microspheres with chitosan two different barriers for the release of the drug encapsulated therein are formed, leading to a reasonable expectation that an impaired release of the encapsulated drug would be achieved.

Accordingly, Applicant submits that it would not have been obvious at the time the claimed invention was made to take the invention of Lee and modify it so as to reach the above-noted features of the present invention, and thus, the rejection of at least independent claims 1 and 29 under 35 U.S.C. § 103(a) is improper and should be withdrawn.

Applicant further submits that the claims 3-5 and 31-33 are allowable at least for the reason that these claims depend on allowable independent claims 1 and 29, respectively, and because these claims recite additional features that further define the present invention.

2. **Rejection over Lee in view of Illum**

As was already discussed above, the primary reference, Lee, is not understood to teach or suggest all of the required elements of Applicant's invention as currently claimed. Furthermore, Illum does not overcome the deficiencies of Lee so as to render Applicant's invention obvious.

As is currently understood, Illum discloses a drug delivery system including an absorption-enhancing material to increase the bioavailability of the encapsulated drug. The preferred materials for increasing the bioavailability of the drugs carried out are phospholipids and lysophasphatidyl compounds. *See, e.g., col. 4, lines 6-12 and 22-30.* The microspheres can be prepared with different kinds of materials, with a preference for starch.

Furthermore, Illum only incidentally considers lysozyme, together with a long list of others, as a possible bioactive compound to be delivered with its drug delivery system. Therefore, it is respectfully submitted that Illum discloses an alternative drug delivery system and its teaching is limited to the addition to microspheres of an absorption-enhancing material to increase the bioavailability of the drug encapsulated therein. Illum is not understood to teach or suggest the drug delivery system of the present invention, even if it could be properly combined with Lee (which has not been admitted), which also does not teach or suggest the use of an absorption-enhancing material.

Accordingly, Applicant submits that no proper combination of Lee and Illum discloses or suggests at least the above-noted features of the present invention, and thus, the rejection of at least independent claims 1 and 29 under 35 U.S.C. § 103(a) is improper and should be withdrawn.

Applicant further submits that the claims 3-5 and 31-33 are allowable at least for the reason that these claims depend on allowable independent claims 1 and 29, respectively, and because these claims recite additional features that further define the present invention.

3. Rejection over Lee in view of Andrianov

As was already discussed above, the primary reference, Lee, is not understood to teach or suggest all of the required elements of Applicant's invention as currently claimed. Furthermore, Andrianov does not overcome the deficiencies of Lee so as to render Applicant's invention obvious. As is currently understood, Andrianov discloses microspheres of alginate as soluble polymer for the delivery of an antigen associated with an adjuvant.

Similar to Illum, as discussed above, Andrianov is directed toward a system for delivering active substances, in this case identified in soluble polymers or polymeric hydrogels optionally cross-linked to form stable microparticles, and not to the active substances to be

delivered. As such, Andrianov merely discloses an alternative drug delivery system and even if it could properly be combined with Lee (which has not been admitted) it would not be obvious to one having ordinary skill in the art to reasonably achieve the results obtained with the microcapsules of Applicant's claimed invention.

Accordingly, Applicant submits that no proper combination of Lee and Andrianov discloses or suggests at least the above-noted features of the present invention, and thus, the rejection of at least independent claims 1 and 29 under 35 U.S.C. § 103(a) is improper and should be withdrawn.

Applicant further submits that the claims 3-5 and 31-33 are allowable at least for the reason that these claims depend on allowable independent claims 1 and 29, respectively, and because these claims recite additional features that further define the present invention.

4. **Rejection over Lee and Andrianov in view of Huang**

As was discussed above, Lee and Andrianov are not understood to teach or suggest all of the required elements of Applicant's invention as currently claims. Furthermore, Huang does not in any way overcome these deficiencies.

In particular, Huang does not appear to be a pertinent document as it appears to be outside of the field in that it discloses food and food additive compositions comprising one or more human milk proteins produced in seeds of transgenic plants, wherein lysozyme is one of the preferred seed-produced proteins. The lysozyme properties discussed in Huang are well known to a person having ordinary skill in the art, since lysozyme has been widely studied and used in therapy as an antiviral since its discovery in 1922. In fact, the properties of lysozyme are exhaustively discussed in the present application on pages 6-7.

Accordingly, Applicant submits that no proper combination of Lee, Andrianov, and Huang discloses or suggests at least the above-noted features of the present invention, and thus, the rejection of at least independent claims 1 and 29 under 35 U.S.C. § 103(a) is improper and should be withdrawn.

Applicant further submits that the claims 3-5 and 31-33 are allowable at least for the reason that these claims depend on allowable independent claims 1 and 29, respectively, and because these claims recite additional features that further define the present invention.

5. **Closing Remarks**

In summary, none of the cited references, either taken alone or in any proper combination, teach or suggest the present invention as currently claimed, which requires a polysaccharide double-layer microcapsule having an outer coating layer of chitosan and an inner layer of alginate mixed with hydroxypropylmethylcellulose, encapsulating the biologically active substance lysozyme. Therefore, one of ordinary skill in the art would not have had a *prima facie* reasonable expectation of success in producing the claimed invention.

This is evidenced, at least in part, by the problems to be solved for an optimal controlled release delivery system for oral administration of bioactive substances. These problems mainly consist of:

a) having an adequate loading of the bioactive substance(s) into microcapsules; and
b) having an adequate release thereof in relation to quantity and time capable of eliciting the desired biological response.

In the present case, the purpose is to provide a delivery system, and in particular a vaccinogenic system, capable of delivering bioactive substances selected from antigens, immunomodulants, chemotherapeutics, cytokines, and growth factors, preferably associated with an adjuvant. In particular, lysozyme can act both as an immunomodulator and an adjuvant. Therefore, lysozyme provides benefits that have not been taught or suggested by the prior art. Furthermore, Applicant's invention, as currently claimed, solves both of the technological problems discussed above. In fact, the presently claimed invention is an improvement over the prior art in regard to both loading and release, as shown by the results reported in Figure 2 and discussed at page 21 of the present application.

Conclusion

Applicant respectfully submits that each and every pending claim of the present invention meets the requirements for patentability under 35 U.S.C. §§ 112, 102, and 103, and respectfully requests that the Examiner indicate allowance of each and every pending claim of the present invention.

In view of the foregoing, it is submitted that none of the references of record, either taken alone or in any proper combination thereof, anticipate or render obvious Applicant's invention as recited in each of claims 1, 3-5, 29, and 31-33. The references of record have been discussed and distinguished, while significant claim features of the present invention have been pointed out.

Accordingly, reconsideration of the outstanding Office Action and allowance of the present application and all the claims therein are respectfully requested and now believed to be appropriate.

If any additional fee is required, please charge Deposit Account Number 19-4330.

Respectfully submitted,

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